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UNTREATED SYPHILIS IN THE MALE NEGRO

Pathologic Findings in Syphilitic and Nonsyphilitic Patients

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THE energies and talents of many people and groups have been contributed in the planning and execution of this long-term study. It has involved a large group of individuals, physically distant from various of the individuals and organizations cooperating in the conduct of the operation. Numerous medical, social, administrative, and financial entities have been coordinated and timed to cover the life span of the study group.

In this paper, the autopsies were performed largely by Dr. J. J. Peters who thus takes the responsibility for the discussions and interpretations of the gross material. Dr. James H. Peers has reviewed personally all of the available tissue with respect to the cardiovascular system and has worked over the findings of his predecessors with respect to the reported microscopic interpretations; thus, he takes full responsibility for the discussion and interpretation of the histologic data.

The study was set up in a manner as to channel all of the autopsy material to the United States Public Health Service, Washington, D. C., for histologic examination. Throughout the years, with changing administrative structures, Dr. R. D. Lillie has been director of the various units working over the material, and has been charged with supervision of the work. Numerous pathology trainees under his supervision, over the years, have made the histologic studies

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Note: This article is one of a series on untreated syphilis in the male Negro which the Venereal Disease Program plans to assemble into a monograph. Single copies of the monograph will be made available upon request to the Venereal Disease Program, Division of Special Health Services, United States Public Health Service, Washington 25, D. C.

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on material as it was submitted, so that the summary, at this stage, rests upon the work of a large number of people whose individual contributions, unfortunately, cannot be identified by name.

Further acknowledgment for invaluable assistance must be given to the following:

The Milbank Memorial Fund, for provision of funds for payment of burial and autopsy expenses, without whose cooperation this study would have been impossible.

The Tuskegee Institute, Tuskegee, Alabama, for administration of the funds locally in payment of burial and autopsy expenses.

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Dr. Murray J. Smith, Health Officer, Tuskegee, Alabama, for local supervision of the program since its inception.

Miss Eunice Rivers, Public Health nurse, whose devotion to the study and to the welfare of this group of patients over the twenty years has been in large part responsible for the opportunity to secure cooperation of the patient and family in permitting post-mortem study.

The various undertaking establishments at Tuskegee, Alabama, whose cooperation has been essential to the success of this phase of the work.

The members of the Division of Venereal Disease, Public Health Service, who in diverse capacities have had responsibility for continued direction of the study and for the gathering and processing of the data.

The serology laboratories, first of the Hygienic Laboratory, United States Public Health Service, and then of the Venereal Disease Research Laboratory for performance of the serologic testing procedures.

In all of these instances, the contributions of time, thought, and energy of many individuals with the full knowledge that the fruits of their efforts would not mature until years later, and in other hands, have been vital. As in all such lifetime studies the devotion of these scientists and public health workers to the search for knowledge for the sake of knowledge and with selflessness must here be acknowledged.

This report provides the first opportunity to correlate pathologic findings with clinical and serologic findings in a group of syphilitic and nonsyphilitic individuals. These individuals are considered in the study of untreated syphilis in the male Negro which has been in process in Macon County, Alabama, since 1932.[1-9] This is familiarly referred to as the Tuskegee Study.

A vast literature has grown up dealing with the pathologic lesions attributed to syphilis. The pathogenesis of certain of the classic syphilitic lesions has been adequately studied and explained. However, there remained, when this study was begun, many gaps in knowledge of the end results of untreated syphilis. It was anticipated that some of remaining problems should be resolved.

No reports of other prospective studies of the end results of untreated syphilis are yet available.

In 1929, Bruusgaard[10] published an analysis of the outcome of the disease in a group of 473 patients at three to forty years after infection. For the first time, data were available to suggest the probability of spontaneous cure, continued latency, or serious or fatal outcome. The Bruusgaard group presently is being restudied with the addition of further autopsy data.[11]

With the appearance of the Bruusgaard paper, the significance of his material was immediately recognized, but certain questions were left unanswered. Plans then were slowly taking shape in the United States for the later development of a national program to control syphilis. It was realized that numerous questions about the natural history and course of syphilis needed answering to provide the necessary scientific background for a program of public health control. As a result of certain factors discussed elsewhere,[12] there was initiated in 1932 in Tuskegee, Alabama, the long-term program of observation of a group of male Negroes with untreated syphilis and a matching control group. The objective was the observation of all individuals through life and to autopsy.

The twenty-year mark, 1952, has passed. By now about one-third of the group originally entered has died; it is anticipated that for the remainder to expire will require at least another twenty years. It is desirable, therefore, to take stock of the findings at this point. We can make available to other workers the results we have noted so that they may be translated into medical and public health practice at once. It is felt that the experience thus far provides important information with particular reference to the effects of syphilis itself. In the years to come, the force of mortality associated with aging will tend to obscure the possible effects of syphilis. This has been shown in the study of life expectancy of this group.[6]

The group now under study consists of 408 syphilitic patients and 192 presumably nonsyphilitic patients. The presence or absence of syphilis at time of entry to the study group was based on medical history, physical examination, and serologic tests of the blood and spinal fluid. Clinical information, collected at periodic examinations during the twenty years the study has been in progress, has furnished evidence that morbidity in a group of untreated male Negroes exceeds that in a nonsyphilitic group, and that abnormal x-ray and fluoroscopic measurements of the heart and aorta occur more frequently in the adult male Negro with untreated syphilis.[8] Life tables constructed on the basis of twenty years of mortality experience in the two groups show that the life expectancy of the Negro man of age 25 to 50 years with untreated syphilis is reduced by about 17 per cent.[5]

To secure the necessary pathologic data, the assistance of the Milbank Memorial Fund was generously offered. This assistance has continued through the present time, permitting the maintenance of a flexible and highly personal program activity in research which would be legally impossible if government funds were to be used, and giving a promise of continuity of support which is vital for such a program. Fees for autopsies and other expenses which official agencies were not able to assume were paid for by the Fund.

However, financial support is only one of the many difficulties involved in securing accurate post-mortem information. The warm climate in this region,

together with the practice of holding bodies for long periods before burial, while relatives assemble, often makes it necessary to embalm the bodies at least by arterial injection before the autopsies are performed. Poor communication facilities contribute to the delay in the examination of fresh tissues. None of the undertaking establishments has refrigeration, and the post-mortem examinations often are made under inconceivably adverse circumstances. Following each gross examination, specimens of the vital organs together with a protocol of the gross findings are forwarded to the Laboratory of Pathology, National Institutes of Health, for microscopic examination.

In the analysis presented in this report, an attempt will be made to determine the extent of agreement in the gross and microscopic findings in relation to the effects of syphilitic infection on the human body and to correlate both types of findings with the clinical and serologic information obtained at the several physical examinations performed on the individual prior to death. Since the validity of such a correlation, especially when it involves conclusions indicating differences among syphilitic and nonsyphilitic patients, depends to a large extent on the accuracy and consistency of the basic data, it might be well to point out some of the following important considerations:

(a) All individuals in the original study group are male Negroes, 25 years of age or older. The syphilitic group was selected first, and the control patients were chosen in such a manner as to obtain comparable age distribution in the two groups.

(b) At the beginning of the study, the 408 syphilitic patients gave a history of infection, with a penile scar as added evidence of infection in some cases, and had at least two positive blood tests for syphilis, or a positive spinal fluid.

(c) Over the twenty-year period all fluoroscopic examinations have been made by one radiologist (Peters), who also has performed most of the gross autopsy examinations. Preparation of histopathologic material has been done by various pathologists at National Institutes of Health during the period of investigation. For purposes of this study, review of each of the gross examinations and of all available microscopic sections of the aortas has been done by one pathologist (Peers) without prior knowledge by him of the patient's history with respect to the presence or absence of syphilis.

(d) The establishment of a syphilitic and a control group by definite criteria at a specific time and the following of each individual clinically and serologically to the time of autopsy has obviated the necessity of doing any portion of the study in retrospect.

During the years 1933 to 1952, 216 of the study group have died: 165 (40 per cent) of the 408 in the syphilitic group, and 51 (27 per cent) of the 192 in the control series. Autopsy has been obtained on 92 (56 per cent) of the deceased syphilitic patients as compared to 33 (65 per cent) of the nonsyphilitic patients who have died. However, no significant differences could be demonstrated in the age of distribution of those autopsied in the two groups (Table I). The fact that age is an equal factor in both groups tends to eliminate from consideration the aging process in accounting for some of the differences in pathologic findings among patients in the study group.

TABLE I. NUMBER AND PERCENTAGE DISTRIBUTION OF SYPHILITIC AND CONTROL PATIENTS EXAMINED AT AUTOPSY, BY AGE AT TIME OF DEATH

AGE AT TIME OF DEATH (YR.)	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
25-34	2	2.2	2	6.2
35-44	4	4.3	1	3.1
45-54	15	16.3	3	9.4
55-64	26	28.3	10	31.2
65-74	24	26.1	8	25.0
75-84	16	17.4	5	15.6
85-94	4	4.3	3	9.4
95 or more	1	1.1	—	—
All ages	92	100.0	32	100.0
Per cent under 65 yr.	51.1		50.0	
Per cent 65 yr. and older	48.9		50.0	
Median age at death	64.5 yr.		63.5 yr.	

CARDIOVASCULAR SYPHILIS

A detailed study of the gross and microscopic autopsy findings on the individuals included in this study indicates that most of the lesions characteristic of syphilitic involvement are to be found in the cardiovascular system. Of the ninety-two syphilitic patients examined post mortem, gross and microscopic findings relative to the cardiovascular system for eighty-nine patients were available for analysis.

Gross Autopsy Examination.—Since one of the major purposes of this study is to investigate the extent to which syphilitic involvement can be measured by gross and microscopic autopsy findings, it seemed advisable to set up diagnostic criteria which would lend consistency and objectivity to the interpretation of the recorded material. While the incidence and description of the gross findings are, of necessity, based on the interpretations recorded by the prosector, the records of the gross examinations have been reviewed and the following conditions have been considered in determining the presence or absence of cardiovascular syphilitic involvement:

(a) Linear striation of the thoracic aorta. Small depressed lineations parallel the long axis of the vessel which may be seen anywhere throughout the aortic length, but which are more numerous and more prominent in the proximal inch of the aorta.

(b) Pearly white scarring of the subintima of the aorta.

(c) Diminution of the elasticity of the aorta in both longitudinal and transverse directions. This observation may be noted where little or no intimal change is apparent.

(d) Fusiform dilatation between the level of the cusps and the junction of the innominate artery, generally on the anterior or anterolateral aspect and disproportionate to any enlargement of the remainder of the aortic lumen.

TABLE II. INCIDENCE BY AGE GROUPS OF ABNORMAL GROSS FINDINGS IN THE AORTAS OF EIGHTY-NINE SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

	SYPHILITIC PATIENTS						CONTROL PATIENTS					
	NUMBER			PER CENT			NUMBER			PER CENT		
	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER
Number of patients examined	89	46	43	—	—	—	32	16	16	—	—	—
Linear striation of thoracic aorta	29	16	13	32.6	34.8	30.2	2	1	1	6.3	6.2	6.2
Pearly intimal scars	26	12	14	29.2	26.1	32.6	6	1	5	18.8	6.2	31.2
Diminution of elasticity	10	3	7	11.2	6.5	16.3	2	—	2	6.3	—	12.5
Fusiform dilatation	40	16	24	44.9	34.8	55.8	14	5	9	43.8	31.2	56.2
Saccular aneurysm of thoracic aorta	7	6	1	7.9	13.0	2.3	—	—	—	—	—	—

(e) Saccular aneurysm, where the dilatation is of sufficient proportions to divert the blood outside the lumen of the aorta, or a widening of sufficient dimensions to produce clot formation and recanalization of the blood flow.

(f) Valvular changes consisting of thickening and rolling of the free edge of the aortic cusps and separation of the valve cusps at the commissures.

On the basis of these criteria, syphilitic aortitis or saccular aneurysm, the most important major manifestations of syphilitic infection, was diagnosed grossly at autopsy in thirty-six (40 per cent) of the eighty-nine patients. From Table II, in which the comparative incidence of the listed criteria among the syphilitic and nonsyphilitic patients is presented, it will be noted that the most reliable gross sign of syphilitic aortitis in this group of patients seems to be linear striation of the intima of the thoracic aorta, a condition found to be present in twenty-nine of the aortas diagnosed as syphilitic. The reliability of this condition as a criterion of syphilitic involvement is based on the facts that definite evidence of this striation was not noted in any case among the syphilitic group where syphilis was not microscopically diagnosed and that only twice was it noted in the thirty-two control patients examined post mortem.

Fusiform dilatation of the thoracic aorta was the most frequent sign of syphilitic involvement, being noted in forty (44.9 per cent) of the aortas in the syphilitic group. However, this dilatation was not considered to be pathognomonic of syphilis since it was found to be present to some degree in four of the aortas in the syphilitic group where, in the absence of other criteria, a diagnosis of syphilitic involvement was not warranted. Furthermore, fusiform dilatation was noted in fourteen (43.8 per cent) of the aortas in the control group, and in six instances was accompanied by moderate or extreme arteriosclerosis, a condition which could result in weakening and stretching of the aortic wall. Intimal scars described as pearly and gross diminution of elasticity were noted somewhat more frequently in the aortas of the syphilitic group than in those of the control group, but the difference in incidence was not marked enough to establish them as reliable diagnostic criteria.

Saccular aneurysm of the thoracic aorta, generally considered to be a pathognomonic lesion of syphilis, was found in only seven of the syphilitic series. Of these, one was small and single, three were small and multiple, two were large enough to have encroached upon and caused bone erosion in the thoracic cage, and one, although small, was the immediate cause of death by rupture into the pericardial sac with cardiac tamponade. No saccular aneurysms were found among the control group. Dissecting aneurysm, a lesion considered to be of arteriosclerotic origin, was found once in the syphilitic and twice in the control group. A single case of aneurysm of the upper abdominal aorta was found in the syphilitic group. In this patient the aorta showed gross arteriosclerosis of an extreme grade and microscopically mild lesions of syphilis; and consequently the aneurysm was considered to be arteriosclerotic in origin.

The findings of gross changes in the aorta must be considered with respect to age as a possible causative factor as well as syphilis. In Table II, a further breakdown of the findings with respect to age is shown. Since the group is not large enough to allow for detailed division, the age of 65 is taken as a significant

landmark. It will be seen that the finding considered along with saccular aneurysm of the thoracic aorta as most highly pathognomonic of syphilis, namely, linear striation of the thoracic aorta, is apparently unaffected by age. In other words, the process appears to be not a result of aging, but instead closely related to syphilis. The other processes, except for saccular aneurysm, show increases with increasing age, which suggests a probable close relationship to the process of aging with attendant changes in structure and function.

Microscopic Examination.—Diagnoses of cardiovascular syphilis on the basis of microscopic findings were made in essentially the same manner as the gross diagnoses, with the pathologist unaware of the presence or absence of history of syphilitic infection and on the basis of diagnostic criteria set up prior to the review of the records. A complete review of the microscopic sections of the aortas was made in light of these diagnostic criteria:

(a) Gross thickening of the aortic wall. Seen easily, when the stained section is viewed with the naked eye, as a fairly uniform thickening of the entire length of the section up to 3 to 5 mm. with blurring of the normal layers. A section of normal aorta so seen appears chiefly as the thin (1 to 2 mm.), uniform, densely stained, medial coat. The arteriosclerotic aorta shows a distinct media and a thickened intima, very irregular in both width and density due to patchy deposition of atheromatous material.

(b) Necrosis of the media. An uncommon but very significant finding consists of irregular stellate or elliptical streaks of infarct type necrosis with nuclear fragmentation in the media, presumably due to occlusion of vasa vasorum, and hence of the nature of miliary gummas.

(c) Fibrosis of the adventitia. In minor degree this is, of course, a subjective interpretation, but when well marked the adventitia is broadened, contributing much to the gross thickening mentioned previously, and the normal loose areolar tissue is converted to quite coarsely fibrous and sometimes partly hyalinized connective tissue.

(d) Scarring of the media. Represents either a healed stage or a lesser degree of the ischemic necrosis noted previously. The elastic laminae of the media are deficient in streaks and patches and replaced by collagenous tissue in which there are often prominent, somewhat dilated, capillary vessels.

(e) Intramural perivascular infiltration consisting of accumulation of variable number of small lymphocytes and some plasma cells about vessels in the media, often those present in medial scars. Some degree of such infiltration also is common in vessels in the somewhat thinned portion of the media underlying large atheromatous masses in the intima.

(f) Thickening of the vasa vasorum. This consists occasionally of endothelial proliferation but more commonly of hyaline fibrosis, greatly thickening the wall and reducing the lumen of the vasa vasorum. It is usually of spotty distribution, often only a few vasa vasorum in a given section being thickened while the remainder appears normal. It cannot be clearly separated from arteriolosclerosis accompanying essential hypertension, and some of the incidence in both syphilitic and control groups may have been due to this common complication.

(g) Adventitial perivascular infiltration. Perhaps "paravascular" infiltration would be a better term for this traditional but unreliable lesion of syphilis. Variable numbers of small lymphocytes and plasma cells are found grouped in relation to adventitial vessels, but more often in patches or small streaks to either side than arranged in a circle about them.

The incidence of these conditions among the syphilitic and control patients is shown in Table III, in order by increasing frequency and correspondingly decreasing specificity. Only two conditions, gross thickening of the aortic wall and necrosis of the media, appeared to be pathognomonic of syphilis, and these two lesions, considered to represent advanced active disease, were in every case accompanied by some of the other microscopic criteria described previously. The increased incidence of the two conditions among the individuals under 65 years of age is added evidence that these lesions are related to the syphilitic rather than the aging process.

In interpreting microscopic slides, some degree of subjective variation is unavoidable, but in general a diagnosis of syphilitic aortitis was made only if two or more of the criteria definitely were present. As noted previously, the histopathologic diagnoses were made and recorded by the pathologist without knowledge of the syphilitic status of the patients. On this basis, syphilitic aortitis was diagnosed in forty-one (46.0 per cent) of the patients in the syphilitic group and in four (12.5 per cent) of those in the control series. However, in the latter series, three of the lesions were doubtful, and one minimal, while those in the syphilitic group consisted of five doubtful, twelve minimal, ten moderate, and fourteen severe.

The attempt to grade the severity of syphilitic involvement of the aorta into four degrees was, like all such attempts at rough quantitation of biologic phenomena, merely an artificial division into four groups of what was actually a continuous spectrum of disease process ranging from the minimal recognizable damage to the most severe, extensive, and fully developed lesions. This grading, however, appears to have some validity since only minimal changes conceivably due to syphilis were observed in the control group, while 60 per cent of the syphilitic group with microscopically diagnosed syphilis presented lesions that were moderate or, even more often, severe.

Comparative Results of Gross and Microscopic Examinations.—The microscopic diagnosis of syphilitic aortitis proved to be slightly more sensitive than the gross diagnosis. Among the eighty-seven aortas examined by both methods, forty were diagnosed microscopically and thirty-five, grossly. In the syphilitic series of cases, the gross and microscopic diagnoses agreed in establishing the presence or absence of syphilitic involvement in sixty-two (71.3 per cent) of the eighty-seven diagnoses compared (in two patients either the gross description or the microscopic material was inadequate for diagnostic purposes). It will be noted from Table IV that in ten instances the gross diagnosis of syphilitic aortitis was not confirmed by the microscopic examination. In two of these the microscopic material, a single slide, was probably insufficient to rule out syphilis. In the remaining eight patients, one almost certainly had arteriosclerosis wrongly interpreted as syphilis, one diagnosis was based on minimal

TABLE III. INCIDENCE, BY AGE GROUPS, OF ABNORMAL MICROSCOPIC FINDINGS IN THE AORTAS OF SEVENTY-NINE SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

	SYPHILITIC PATIENTS						CONTROL PATIENTS					
	NUMBER			PER CENT			NUMBER			PER CENT		
	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER
Number of patients examined	89	46	43	—	—	—	32	16	16	—	—	—
Gross thickening of aortic wall	12	7	5	13.5	15.2	11.6	—	—	—	0	0	0
Necrosis of the media	7	5	2	7.9	10.9	4.7	—	—	—	0	0	0
Fibrosis of the adventitia	28	13	15	31.5	28.3	34.9	3	2	1	9.4	12.5	6.3
Medial scars	30	15	15	33.7	32.6	34.9	4	1	3	12.5	6.2	18.8
Intramural perivascular infiltration	33	17	16	37.1	37.0	37.2	5	2	3	15.6	12.5	18.8
Thickened vasa vasorum	37	20	17	41.6	43.5	39.5	6	3	3	18.8	18.8	18.8
Adventitial perivascular infiltration	58	30	28	65.2	65.2	65.1	13	6	7	40.6	37.5	43.8

evidence of syphilis in the form of a few longitudinal striae, and in the other six patients there was moderate to extreme arteriosclerosis with scarring and some dilatation of the aorta which had been attributed to syphilis rather than to arteriosclerosis. From the same table it is apparent that the diagnosis of syphilitic aortitis in fifteen patients was made by microscopic examination alone, but in ten of these the lesions were minimal or doubtful and would not have been expected to be accompanied by gross changes. In thirty-seven (41.6 per cent) of the syphilitic group, there was neither gross nor microscopic evidence of syphilitic aortitis, and in twenty-five patients (28.1 per cent), aortitis was diagnosed by both gross and microscopic findings.

TABLE IV. COMPARISON OF THE INCIDENCE OF SYPHILITIC INVOLVEMENT OF THE CARDIOVASCULAR SYSTEM AS DIAGNOSED FROM GROSS AND MICROSCOPIC FINDINGS AMONG EIGHTY-SEVEN SYPHILITIC PATIENTS EXAMINED AT AUTOPSY

MICROSCOPIC EXAMINATION DIAGNOSIS	GROSS EXAMINATION DIAGNOSIS	
	CARDIOVASCULAR SYPHILITIC INVOLVEMENT	NO CARDIOVASCULAR SYPHILITIC INVOLVEMENT
Cardiovascular syphilitic involvement	25	15
Doubtful	—	5
Minimal	7	5
Moderate	5	4
Severe	13	1
No cardiovascular syphilitic involvement	10	37

Aortitis in Relation to Positive Serologic Tests.—Of the eighty-seven patients in whom the aorta was examined both grossly and microscopically, sixty had positive blood serologic tests for syphilis when last tested (Kahn qualitative) prior to death, three had doubtful tests, and twenty-four showed negative results (Table V). Of the sixty with positive tests, twenty-three were diagnosed by both gross and microscopic methods as having syphilitic aortitis, five by gross examination only, and nine by microscopic examination only. If, in order to be conservative, it is assumed that none of the fourteen with only gross or only microscopic evidence, and thus possibly nonsyphilitic, had true syphilitic involvement, the minimum incidence of cardiovascular syphilis among persons with sustained seropositivity from time of entry to study until death would be 38 per cent. On the other hand, if all fourteen of those with a possible questionable diagnosis had syphilitic involvement, the maximum incidence of cardiovascular syphilis in this same group would be 62 per cent. On the basis of these two estimates of the incidence of aortitis in the group coming to autopsy, it is suggested that a Negro male with syphilis of more than ten years' duration for which he had received no treatment (or less than 12 units of routine treatment when a unit is defined as one injection of an arsenical or two of bismuth) and with sustained seropositivity prior to death would have roughly a 50-50 chance of demonstrating syphilitic cardiovascular involvement at autopsy.

TABLE V. THE INCIDENCE OF SYPHILITIC AORTITIS AS DIAGNOSED BY GROSS AND/OR MICROSCOPIC EXAMINATION IN RELATION TO SEROLOGIC STATUS PRIOR TO DEATH

RESULTS OF LAST SEROLOGIC TEST PRIOR TO DEATH (KAHN QUALITATIVE)	TOTAL CASES EXAMINED	GROSS AND MICROSCOPIC	GROSS ALONE	MICROSCOPIC ALONE	ABSENCE OF AORTITIS ESTABLISHED BY GROSS AND MICROSCOPIC
Positive	60	23	5	9	23
Doubtful	3	—	—	—	3
Negative	24	2	5	6	11
Total	87	25	10	15	37

The presence of aortitis was not confirmed by either gross or microscopic examinations in the three patients with doubtful serologic test on the blood at last test prior to death. Of the twenty-four negative serologic tests prior to death, only two individuals were diagnosed both grossly and microscopically as having syphilitic aortitis by either gross or microscopic examination. The remaining eleven seronegative individuals showed freedom from syphilitic aortitis by both gross and microscopic means.

Cardiac Hypertrophy.—The heart of the patient with syphilis may be enormously enlarged, moderately enlarged, or not enlarged at all. With the exception of syphilitic valvulitis, there is no gross finding of sufficient specificity to justify a diagnosis of hypertrophy due to syphilitic involvement. Considering as hypertrophied all hearts weighing 400 grams or more, it was found that forty-eight (69.5 per cent) of the sixty-nine hearts weighed at autopsy among the syphilitic patients were enlarged as compared to eighteen (69.2 per cent) of the twenty-six weighed in the control group. On the basis of the equal incidence of cardiac hypertrophy in the two groups, it would seem that in this study group, at least, the abnormality is not related to syphilitic involvement. In attempting to account for the high incidence of cardiac enlargement in the study population, the presence of other abnormal conditions, including hypertension, was investigated. Among those whose heart weight was less than 400 grams, 20.7 per cent had systolic blood pressures of 160 mm. of mercury or more when last examined prior to death as compared to 54.7 per cent of those where the heart weight was 400 grams or more. Diastolic pressures of 95 mm. of mercury or more were found in 37.9 per cent of those with heart weight less than 400 grams and in 54.7 per cent of those with heart weight of 400 grams or more. The massively hypertrophied hearts weighing over 600 grams were found decidedly more often in the control group. By the most liberal interpretation of the autopsy records, slightly less than 10 per cent of the entire syphilitic group showed aortic valve lesions suggestive of syphilis, and only one-half of these were reasonably pathognomonic. In the combined groups of syphilitic and control patients there were no instances of rheumatic valvulitis, congenital anomaly, or pericardial adhesions. Thus, it would seem that syphilis played a minor role in the causation of cardiac

hypertrophy and that the principal etiological factors probably were hypertension and/or myocardial degeneration and compensatory hypertrophy. The degrees of longevity and of physical activity in these patients with massive hypertrophy are remarkable, as discussed elsewhere.[6,7]

The Incidence of Arteriosclerosis.—The similarity of the cardiovascular signs of arteriosclerosis and syphilitic aortitis has led to much speculation regarding the degree of coincidence of the two conditions. Clinicians are in agreement that if syphilis predisposes to severe arteriosclerosis or is responsible for premature arteriosclerotic involvement, pathologic evidence is needed before such a premise can be accepted.

The incidence of arteriosclerosis as detected by gross examination among the syphilitic and nonsyphilitic patients by age at time of death is shown in Table VI. On cursory examination, the number of cases of advanced arteriosclerosis among those patients under 55 years of age in the syphilitic group is quite startling but, due to the smallness of the number examined among the younger individuals, the difference in the incidence of arteriosclerosis among the younger individuals in the two groups is not statistically significant. The increased proportion of severe arteriosclerosis in both the syphilitic and the nonsyphilitic groups with the progression of age is to be expected in view of the known correlation of arteriosclerosis with age. The grading or degree of involvement is subject to the same general considerations as discussed with respect to syphilitic involvement earlier in this paper.

Clinical Findings Related to Autopsy Findings.—In the correlation of clinical findings prior to death with the gross and microscopic autopsy findings, only those cases were used where both gross and microscopic examinations were in agreement in establishing or ruling out the presence of syphilitic involvement. This selection of cases was necessary since clinical diagnostic methods could not be expected to detect minimal changes which could be diagnosed only by microscopic methods nor did it seem reasonable to attempt to correlate clinical findings with gross diagnoses which had not been verified by microscopic methods. Presented in Table VII is a summary of the clinical findings including those diagnosed by x-ray and fluoroscopic methods in relation to gross and microscopic findings among the selected group of syphilitic individuals described previously.

In the gross and microscopic autopsy examination, two aortas were found to have syphilitic involvement where none had been noted by physical examination or x-ray examination. In one of these instances a clinical diagnosis of aortic abnormality and cardiac hypertrophy (the heart weighed 1,000 grams at autopsy) due to rheumatic heart disease was recorded. In the other patient the aorta was described as normal at the last examination prior to death; however, this examination was performed in 1938 and the patient died in 1948, a ten-year interval during which aortic involvement might well have become manifest.

The presence of six of the seven saccular aneurysms found at autopsy had been detected by clinical means prior to death. The patient in whom the diagnosis was not made was seen only at the time of the initial physical examination

TABLE VI. THE INCIDENCE OF ARTERIOSCLEROSIS AMONG SYPHILITIC AND NONSYPHILITIC PATIENTS BY DEGREE OF INVOLVEMENT AND AGE AT TIME OF DEATH

AGE AT TIME OF DEATH (YR.)	SYPHILITIC PATIENTS					NONSYPHILITIC PATIENTS				
	NONE OR DOUBTFUL	MINIMAL	MODERATE	SEVERE	NOT EXAMINED	NONE OR DOUBTFUL	MINIMAL	MODERATE	SEVERE	NOT EXAMINED
25-34	2	—	—	—	—	1	1	—	—	1
35-44	2	1	1	—	—	—	1	—	—	—
45-54	2	5	6	2	—	1	1	3	4	1
55-64	1	8	9	4	1	1	1	—	6	—
65-74	2	3	13	4	—	—	1	3	2	—
75-84	—	2	9	6	—	—	—	—	2	1
85-94	—	1	3	1	—	—	—	—	—	—
95 or older	—	—	1	—	—	—	—	—	—	—

in 1932 and was described at that time as having a marked fusiform aortic dilatation. Since death did not occur until four years later, in 1936, this too could have been an instance where the aneurysm developed during the interval between physical examination and death. It has been possible for one of the authors (Peters) to observe in a series of four syphilitic patients the gradual progression from normal aortic configuration through dilatation to development of aneurysm.

TABLE VII. COMPARISON OF CLINICAL DIAGNOSES INVOLVING THE AORTA PRIOR TO DEATH WITH DIAGNOSES BASED ON GROSS AND MICROSCOPIC FINDINGS AMONG SIXTY-TWO SYPHILITIC PATIENTS AMONG WHOM THE GROSS AND MICROSCOPIC DIAGNOSES WERE IN AGREEMENT

CLINICAL DIAGNOSIS PRIOR TO DEATH	GROSS AND MICROSCOPIC DIAGNOSIS		
	SYPHILITIC AORTITIS	SACCULAR ANEURYSM	NO SYPHILITIC AORTIC INVOLVEMENT
Syphilitic aortitis	16	1	19
Saccular aneurysm	—	6	—
No syphilitic aortic involvement	2	—	18
Total	18	7	37

The nineteen patients in whom aortitis was diagnosed clinically, yet in whom the gross and microscopic examinations ruled out the presence of syphilitic involvement of the aorta, offer proof of the fact that clinical methods are effective in the detection of abnormality but inadequate in the determination of etiology. Eight of the nineteen patients diagnosed with aortitis by clinical methods only were described at gross examination as having arteriosclerosis with fusiform dilatation of the aorta, one patient was found to have a dissecting aneurysm, nine were described as having moderate or severe arteriosclerosis, and only one patient was reported as completely negative for arteriosclerosis.

CENTRAL NERVOUS SYSTEM INVOLVEMENT

The central nervous system (brain and portion of spinal cord) was examined in forty-six of the syphilitic patients and in thirteen of the control patients (Table VIII). Of the forty-six brains of syphilitic patients, twenty-eight were found to be essentially normal, six showed one or more areas of arteriosclerotic softening, five showed cerebral hemorrhage, including one traumatic hemorrhage secondary to skull fracture, and one toxic petechial hemorrhage apparently secondary to lobar pneumonia. An abscess secondary to bacterial endocarditis was found in one instance. Of the twenty-nine patients in whom sclerosis of the major arteries was detected, only three were sufficiently advanced to be especially noted. Only two brains of the forty-six examined showed definite syphilitic involvement, the one meningovascular syphilis, and the other paresis. Both of the patients with definite involvement died as inmates of the state insane hospital. The patient with meningovascular syphilis showed only minimal

microscopic evidence of aortitis, but the paretic patient showed a typical full-blown gross and microscopic picture of syphilitic aortitis. The great scarcity of frank syphilitic involvement of the central nervous system and the complete absence of lesser lesions attributable to syphilis are noteworthy.

TABLE VIII. INCIDENCE OF ABNORMAL CONDITIONS IN THE CENTRAL NERVOUS SYSTEM AMONG FORTY-FOUR SYPHILITIC AND THIRTEEN CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Opacity of pia-arachnoid	9	20.5	1	7.7
Focal softening of cortex	5	11.4	—	—
Focal softening of white matter	2	4.5	—	—
Cerebral hemorrhage	5	11.4	1	7.7
Sclerosis of major arteries	29	65.9	6	46.2
Microscopic cortical atrophy	2	4.5	—	—
Cellular infiltration, perivascular and meningeal	7	15.9	1	7.7
Perivascular iron pigment	2	4.5	—	—
Glial nodules on the ependyma	1	2.3	1	7.7

Of the thirteen brains from control patients examined, nine were essentially normal. Two of the six patients showing arteriosclerosis had damage severe enough to be especially noted; one showed cerebral hemorrhage and another edema secondary to head injury. A mild degree of grossly visible thickening of the pia-arachnoid was noted in a few cases in both syphilitic and control series, but it could not be correlated with microscopic lesions and was of no apparent pathologic significance.

While only two of the forty-six syphilitic patients having examinations of the brain and spinal cord showed unequivocal evidence of syphilitic involvement of the central nervous system, comparison between syphilitic and nonsyphilitic groups (the material presented in Table VIII) reveals a higher proportion of abnormal findings in the syphilitic group. However, no particular significance can be attached to these findings due to the small number of brain examinations made at autopsy, especially among the controls.

OTHER SYSTEMS OF THE BODY

From the findings of this study, it would seem that the systems of the body, other than the cardiovascular and the central nervous systems, are not commonly affected by syphilitic infection. In Table IX is shown the comparative incidence of pertinent findings in the respiratory system in the two groups of patients. While fibrosis of the lung was found more often among the ninety-two syphilitic patients and pleural effusion was present to a greater extent among the thirty-two control patients, neither difference showed statistical significance. The incidence of hypostatic or bronchopneumonia was high in both groups, and was a terminal illness in patients for whom the primary cause of death was assigned to other disease processes.

TABLE IX. INCIDENCE OF ABNORMAL CONDITIONS IN THE RESPIRATORY SYSTEM AMONG NINETY-TWO SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Stenosis or destruction in respiratory system	1	1.1	—	—
Scars, masses, or cavities in lung—tuberculous	6	6.5	2	6.2
Scars, masses, or cavities in lung—nontuberculous	4	4.3	—	—
Lobar pneumonia	4	4.3	4	12.5
Hypostatic or bronchopneumonia	43	46.7	11	34.4
Pleural effusion	48	52.2	20	62.5
Fibrosis of lung	38	41.3	9	28.1
Malignant tumors	—	—	2	6.2

It will be noted from Table XIII that four of the syphilitic group died from diseases involving the gastrointestinal system. In each instance, only laboratory evidence of syphilis was noted and no clinical symptoms of syphilitic involvement were present prior to death. At autopsy, one patient showed diffuse cirrhosis of the liver; another, fatty infiltration of the liver; the third patient, a pancreatic cyst and hemangioma of the liver; and the fourth, peptic ulcer with fatty infiltration of the liver. While some involvement of the liver was noted in each of these cases, the morbid processes could not be directly attributed to syphilitic infection.

Fibrosis of the pancreas, thought by some investigators (as reviewed by Rosahn[13]) to be one of the characteristic lesions of late syphilitic involvement, was noted in five of the syphilitic group at autopsy. In one instance, the fibrosis was associated with a duodenal ulcer, and in another, arteriosclerotic changes were thought to have taken place. The remaining three patients exhibited fibrosis which could not be attributed to a nonsyphilitic cause. However, all five patients, representing the presence of fibrosis in 5.3 per cent of the syphilitic group, do not constitute a significantly higher incidence in the syphilitic population. In all, only slight differences in the incidence of abnormal gastrointestinal findings were noted among the syphilitic and the nonsyphilitic patients (Table X).

Comparatively few abnormal findings were found at autopsy in the hematopoietic and endocrine systems. Capsular opacity and thickening of the spleen, the only findings of any consequence, were present at about the same degree in both the syphilitic and the control groups. A sickle-cell trait was exhibited in approximately 3 per cent of each group (Table XI).

The incidence of glomerulonephritis, pyelonephritis, and cystitis was higher among the syphilitic patients, but in each instance the difference between the number of urinary infections in the two study groups is less than that which could be attributed to chance occurrence. More than 50 per cent of both groups showed some degree of arteriosclerotic involvement of the urinary system, and in many cases this involvement led to renal failure and death.

Atrophy and scarring of the testis have been considered by some authorities to be pathognomonic of syphilitic infection. In this study, atrophy was noted

in almost 50 per cent of each of the study groups (Table XII). Since roughly 50 per cent of each group were 65 years of age or older at time of death, it seemed quite possible that testicular atrophy might be merely an aging process in this population. On investigation, this assumption was considered to be valid in that 31 per cent of the syphilitic patients and 29 per cent of the control patients under 65 years exhibited the condition, as compared to 65 per cent of each group among those 65 years and older. Scarring of the testis was noted in six individuals, all of them in the syphilitic group; in one instance, however, the condition was thought to be a tuberculous process. At any rate, the incidence of the lesion among the syphilitic patients is within the limits of chance.

TABLE X. INCIDENCE OF ABNORMAL CONDITIONS IN THE DIGESTIVE SYSTEM AMONG NINETY-TWO SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Esophageal varices	—	—	—	—
Atrophy of the gastric mucosa	—	—	—	—
Chronic gastritis	1	1.1	1	3.1
Peptic ulcer	3	3.3	—	—
Malignant tumors of gastrointestinal tract	3	3.3	1	3.1
Rectal stricture	—	—	—	—
Fatty infiltration of liver	21	22.8	9	28.1
Gross scarring of liver (hepar lobatum)	4	4.3	2	6.2
Gumma of liver	—	—	—	—
Diffuse cirrhosis of liver	14	15.2	6	18.8
Fibrosis of pancreas	5	5.4	—	—

TABLE XI. INCIDENCE OF ABNORMAL CONDITIONS IN THE HEMATOPOIETIC AND ENDOCRINE SYSTEMS AMONG NINETY-TWO SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Hematopoietic system:				
Enlargement of spleen	10	10.9	2	6.2
Infarct of spleen	2	2.2	—	—
Capsular opacity and thickening of spleen	36	39.1	12	37.5
Sickle-cell trait	3	3.3	1	3.1
Blood dyscrasias (leukemia)	1	1.1	—	—
Endocrine system:				
Pituitary pathologic changes	—	—	1	3.1
Thyroid hyperplasia—diffuse	1	1.1	—	—
Thyroid hyperplasia—nodular	—	—	—	—
Adrenal pathologic changes	5	5.4	3	9.4

In this particular study group it was difficult to establish the presence of syphilitic involvement by means of external post-mortem examination. Alopecia

areata, while fairly prevalent in the group, was not sufficiently defined to differentiate the syphilitic from the control patients. Osteitis was noted in four (4 per cent) of the syphilitic group, but was not severe or extensive enough to establish definitely that it was of syphilitic origin. Pigmented scars were frequently seen over the anterior aspects of the legs. However, they could not be distinguished in many patients from healed varicose ulcerations or from similar scarred areas resulting from long exposure to the heat of an open fireplace, a common method of heating in the study area. Where pigmentation of the palms of the hands was found it was difficult to determine if the pigmented areas were healed lesions of secondary syphilis or were caused by long exposure to the sun. Enlarged lymph nodes were found with equal frequency in the two groups.

TABLE XII. INCIDENCE OF ABNORMAL CONDITIONS IN THE URINARY AND REPRODUCTIVE SYSTEMS AMONG NINETY-TWO SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Urinary system:				
Arteriosclerotic atrophy of kidney	1	1.1	—	—
Arteriosclerosis—benign	52	56.5	16	50.0
Arteriosclerosis—malignant	1	1.1	1	3.1
Glomerulonephritis	18	19.6	4	12.5
Pyelonephritis	22	23.9	3	9.4
Cystitis	15	16.3	5	15.6
Malignant tumors	—	—	—	—
Reproductive system:				
Prostatic hypertrophy	59	64.1	18	56.2
Atrophy of testis	43	46.7	15	46.9
Scarring of testis	5	5.4	—	—
Gumma of testis	—	—	—	—
Stricture of urethra	2	2.2	—	—
Malignant tumors	5	5.4	—	—

RELATIONSHIP OF CLINICAL DIAGNOSIS TO PRIMARY CAUSE OF DEATH

A general idea of the relationship of the clinical diagnosis prior to death and the primary cause of death as determined through autopsy examination can be gained from the material shown in Table XIII. The four patients (4 per cent of the syphilitic group) in whom no clinical evidence was noted, yet in whom cardiovascular syphilis was recorded as the disease process causing death, provided a rough estimate of the inefficiency of present clinical methods in the diagnosis of syphilitic cardiovascular conditions severe enough to cause death. Of the syphilitic group, fifty-two were clinically diagnosed with cardiovascular involvement; in twenty-one (40 per cent) of these patients the syphilitic process was determined by post-mortem examination to be the underlying cause of death. The eleven individuals having clinical evidence of central nervous system involvement included the following: three with clinical paretic symptoms, where

TABLE XIII. PRIMARY CAUSE OF DEATH BASED ON AUTOPSY FINDINGS AMONG THIRTY-TWO CONTROL PATIENTS AND AMONG NINETY-TWO SYPHILITIC PATIENTS BY CLINICAL SYPHILIS DIAGNOSIS AND SEROLOGY STATUS PRIOR TO DEATH

PRIMARY CAUSE OF DEATH	CONTROL PATIENTS	SYPHILITIC PATIENTS—CLINICAL DIAGNOSIS AND SEROLOGY									
		NO CLINICAL EVIDENCE		CARDIOVASCULAR SYPHILIS		CNS SYPHILIS		CARDIOVASCULAR AND CNS SYPHILIS		BONE AND SKELETAL SYPHILIS	
		STS+	STS−	STS+	STS−	STS+	STS−	STS+	STS−	STS+	STS−
Cause related to syphilis	—	4	—	18	2	1	2	—	1	—	—
Aortitis, associated with congestive heart failure	—	3	—	11	2	—	1	—	1	—	—
Aneurysm	—	1	—	6	—	—	—	—	—	—	—
Valvular disease	—	—	—	1	—	—	—	—	—	—	—
Paresis	—	—	—	—	—	1	1	—	—	—	—
Tabes dorsalis	—	—	—	—	—	—	—	—	—	—	—
Tuberculosis, respiratory	1	2	—	2	—	—	—	—	—	—	—
Tuberculosis, other	—	1	—	—	—	—	—	—	—	—	—
Malignant neoplasm	4	5	—	2	1	—	—	1	—	—	—
Arteriosclerosis and degenerative heart disease	9	4	2	4	2	—	—	—	1	—	—
Hypertension	—	1	1	—	—	—	—	—	—	—	—
Vascular lesions of CNS	—	2	—	—	—	—	—	—	—	—	—
Pneumonia	1	—	—	—	—	—	—	—	—	—	—
Gastrointestinal disease	—	4	—	—	—	—	—	—	—	—	—
Renal failure	13	6	—	11	2	1	—	2	1	2	—
Motor vehicle accident	—	—	—	—	—	—	—	—	1	—	—
Other accidents	4	1	1	1	—	—	—	—	—	—	—
All causes	32	30	4	38	7	2	2	3	4	2	—

STS—Serologic test for syphilis.

paresis was established as the cause of death in two cases, and cardiovascular syphilis in the other; eight in whom eye involvement, vascular changes, or tabetic symptoms or signs were noted, but who died of nonsyphilitic causes. The distribution of the causes of death among the syphilitic patients, aside from syphilis itself, does not seem to be different from that in the control group. Four of the control patients (12 per cent) as compared to nine of the syphilitic patients (10 per cent) died from cancer; one member of the control group (3 per cent) and six individuals in the syphilitic group (7 per cent) succumbed to tuberculosis.

SUMMARY

1. A study of the comparative incidence of the morphologic lesions found among ninety-two untreated syphilitic patients and thirty-two control patients examined at autopsy is presented.

2. The gross and microscopic findings on the individuals included in this study indicate that the lesions characteristic of syphilitic involvement in the Negro male are to be found for the most part in the cardiovascular system. For this reason, a detailed analysis of the cardiovascular abnormalities, including the relationship of clinical and autopsy findings, is included.

3. Linear striation of the thoracic aorta was found to be the most reliable gross sign of syphilitic aortitis, while thickening of the aorta wall and necrosis of the media were found to be pathognomonic of syphilitic aortitis in the microscopic examination.

4. In thirty-seven (41.6 per cent) of the eighty-seven syphilitic patients in whom the aorta was examined grossly and microscopically, there was no evidence of syphilitic aortitis by either examination, and in twenty-five (28.1 per cent) of the patients, aortitis was diagnosed by both gross and microscopic findings.

5. On the basis of the findings in this study, it is estimated that a Negro male with syphilis of more than ten years' duration for which he had received no treatment (or less than 12 units of routine treatment) and with sustained seropositivity prior to death would have, roughly, a 50-50 chance of demonstrating syphilitic cardiovascular involvement at autopsy.

6. The unusually high prevalence of cardiac hypertrophy in this study group is believed to be due to the presence of compensatory hypertrophy caused by hypertension and/or myocardial degeneration.

7. The similarity of the clinical signs and symptoms of syphilitic and arteriosclerotic aortitis reduces the efficiency of clinical methods in the detection of syphilitic aortitis.

8. The brain was examined in forty-six of the ninety-two syphilitic patients autopsied. The two patients showing clinical symptoms of central nervous system involvement (paresis and meningovascular syphilis) were among the group examined. The patient diagnosed with meningovascular syphilis showed microscopic cortical atrophy at autopsy, and both patients were found to have opacity of the pia-arachnoid and perivascular and meningeal cellular infiltration.

9. In the respiratory, digestive, hematopoietic, endocrine, urinary, and reproductive systems of the human body, the incidence of abnormalities among syphilitic patients was not significantly different from that among the control patients.

10. In twenty-eight (30.4 per cent) of the ninety-two syphilitic patients examined at autopsy, syphilitic involvement of the cardiovascular or the central nervous system was established as the primary cause of death. The distribution of the causes of death among the syphilitic patients, aside from syphilis itself, was not different from that in the nonsyphilitic group.

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